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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

SPRINGER *et al.*

Appl. No. 08/474,388

Filed: June 7, 1995

For: **ICAM-1 Preparations**

Art Unit: 1644

Examiner: Gambel, P.

Atty. Docket: 1011.004000D/SLF/RCM

Appeal Brief Under 37 C.F.R. § 1.192

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I. Introduction

This is an Appeal from the final rejection of claims 71-73, 75-78, 80-82 and 99 for the above-captioned U.S. Patent Application for which a Notice of Appeal was filed on March 21, 2002. Appellants hereby file their Appeal Brief in triplicate as required under 37 C.F.R. § 1.192(a). Also submitted herewith is the $320.00 fee for filing an Appeal Brief as set forth in 37 C.F.R. § 1.17(c).

II. Real Party in Interest (37 C.F.R. § 1.192(c)(1))

The real parties in interest in this matter are the Dana Farber Cancer Institute, assignee of record of all right, title and interest in the above-captioned application, as demonstrated by the Assignment and attendant documents executed on August 27, 1990 (Reel 5411, Frame 0847), and Boehringer Ingelheim Pharmaceuticals, Inc., a licensee of the above-captioned application.

III. Related Appeals and Interferences (37 C.F.R. § 1.192(c)(2))

Appellants, including the undersigned legal representative and the assignee of the above-captioned application, are aware of no pending interference which will directly affect, or be directly affected by, or have a bearing on the decision by the Board of Patent Appeals and Interferences ("the Board") in the pending appeal.

IV. Status of the Claims (37 C.F.R. § 1.192(c)(3))

The above-captioned application was filed as a divisional application of prior Application No. 08/186,456, on June 7, 1995, with a total of 70 claims. In a preliminary amendment filed

concurrently with the application, claims 1-15, 24-26 and 45-68 were canceled. Claims 16-23, 27-44 and 69-70 remained pending.

In the Office Action of August 7, 1996 (Paper No. 3), the Examiner restricted the claims into Groups I-VII. In an Amendment and Response to Restriction Requirement filed on January 7, 1997, Appellants elected to prosecute the invention of Group I to ICAM-1 proteins, canceled claims 16-23, 27-44 and 69-70, and added new claims 71-86.

In the Office Action of April 15, 1997 (Paper No. 6), the Examiner rejected claims 71-86 under 35 U.S.C. § 112, first and second paragraph. In addition, claims 71-79, 80-83 and 84-86 were rejected under 35 U.S.C. § 102(a), 35 U.S.C. § 102(b), and 35 U.S.C. § 103(a). Claims 71-79, 84 and 86 were also rejected under 35 U.S.C. § 102(e). In an Amendment and Response filed on October 15, 1997, Appellants canceled claims 84-86, amended claims 73 and 81, and added new claims 87-98.

In a Final Office Action mailed January 6, 1998 (Paper No. 9), the Examiner indicated that new claims 87-98 were withdrawn from consideration. The Examiner maintained in part the 35 U.S.C. § 112, second paragraph, rejection of claims 71-83, maintained the 35 U.S.C. § 112, first paragraph, rejection of claims 71-83, as well as the rejection of claims 71-79 and 86 under 35 U.S.C. § 102(a) or (b), and the rejection of claims 71-79 under 35 U.S.C. § 102(e). Appellants filed an Amendment and Reply Under 37 C.F.R § 1.116 on July 6, 1998, canceling claim 74 and amending claims 71, 75-78, 80 and 81.

The Examiner's Advisory Action of July 31, 1998 (Paper No. 12), indicated that, in view of Appellants' communication of July 6, 1998, the rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102(a) and (b) were withdrawn. However, the Examiner maintained

the rejection of claims 71-83 under 35 U.S.C. § 102(e). The Examiner also indicated that Appellants' Amendment filed July 6, 1998, would not be entered.

Appellants filed a Notice of Appeal from the Examiner to the Board of Patent Appeals and Interferences on July 6, 1998, and a Submission Under 37 C.F.R. § 1.129(a) on September 8, 1998, requesting that the Final Rejection of January 6, 1998, be withdrawn and that the Amendment filed July 6, 1998, be entered.

In the Office Action of November 23, 1998 (Paper No. 14), the Examiner rejected claims 73 and 79 under 35 U.S.C. § 112, fourth paragraph. The Examiner additionally rejected claims 71-73, 74-78 and 80-83 under 35 U.S.C. § 112, first paragraph, claims 71-73 and 79 under 35 U.S.C. § 102(b), claims 71-73 and 75-79 under 35 U.S.C. § 103(a) as allegedly obvious over Tomassini, thesis 8624033 (1986) [hereinafter "Tomassini thesis"], in view of Tomassini *et al.*, *J. Virol. 58*:290-295 (1986) [hereinafter "Tomassini article"], and claims 80 and 81 under 35 U.S.C. § 102(b). In an Amendment and Reply Under 37 C.F.R. § 1.111 filed May 24, 1999, Appellants canceled claims 79, 83 and 87-98 and amended claims 71, 74, 80 and 81.

In the Final Office Action of August 4, 1999 (Paper No. 17), the rejection of claims 73 and 79 under 35 U.S.C. § 112, fourth paragraph, and claims 71-73, 74-78 and 80-83 under 35 U.S.C. § 112, first paragraph, was withdrawn. However, the Examiner maintained the rejection of claims 71-73 and 80-82 under 35 U.S.C. § 102(b) and claims 71-73 and 75-78 under 35 U.S.C. § 103(a). The Examiner also newly rejected claims 80-82 under 35 U.S.C. § 112, first paragraph.

On February 4, 2000, Appellants filed an Amendment and Reply Under 37 C.F.R. § 1.116 (adding new claim 99 (was misnumbered as claim 83)) and a Notice of Appeal from the Examiner to the Board of Patent Appeals and Interferences.

The Examiner's Advisory Action of February 18, 2000 (Paper No. 21), indicated that claims 71-73, 75-78, 80-82 and 99 were rejected "for the rejections of record (see sections 7+8 of Paper No. 17)." Sections 7 and 8 refer to rejections under 35 U.S.C. § 102(b) as anticipated by the Tomassini thesis or the Tomassini article, and under 35 U.S.C. § 103(a) as allegedly obvious over the Tomassini thesis in view of the Tomassini article. The Examiner further indicated that the Amendment filed on February 4, 2000, would be entered upon the filing of an appeal.

Appellants filed a second Submission Under 37 C.F.R. § 1.129(a) on September 5, 2000, requesting that the Final Rejection of August 4, 1999, be withdrawn, and requested an interview with the Examiner on October 3, 2000. In the Interview Summary (Paper No. 24), the Examiner indicated, *inter alia*, that Appellants would "consider filing a declaration to distinguish claims from prior art." On October 24, 2000, Appellants had hand-carried to the Examiner a Supplemental Amendment Under 37 C.F.R. § 1.111 and an executed Declaration of Dr. Robert Rothlein under 37 C.F.R. § 1.132. On December 6, 2000, at the Examiner's request, Appellants also had hand-carried a copy of prior Application No. 07/045,963.

In the Office Action of December 15, 2000 (Paper No. 28), the Examiner rejected claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 112, first paragraph, claims 75-78 and 80-82 under 35 U.S.C. § 112, second paragraph, and rejected claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 102(b) as anticipated by the Tomassini thesis, the Tomassini article or Colonno *et al.*, Viral Attachment and Entry into Cells, Proceedings of an ASM Conference, Philadelphia, PA, April 10-13, 1985 [hereinafter "Colonno"], and under 35 U.S.C. § 103(a) as allegedly obvious over the Tomassini thesis and/or the Tomassini article and/or Colonno. On June 15, 2001,

Appellants filed an Amendment and Reply under 37 C.F.R. § 1.111, amending claim 80.

In the Final Office Action of September 21, 2001 (Paper No. 30), the Examiner withdrew the rejection of claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 112, first paragraph.[1] However, the Examiner maintained the rejection of 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 102(b) as anticipated by the Tomassini thesis, the Tomassini article or Colonno, and under 35 U.S.C. § 103(a) as allegedly obvious over the Tomassini thesis in view of the Tomassini article and/or Colonno. Appellants filed a Reply under 37 C.F.R. § 1.116 and a Notice of Appeal from the Board of Patent Appeals and Interferences on March 21, 2002.

In the Advisory Action of April 1, 2002 (Paper No. 33), the Examiner maintained the rejections of the claims "for the reasons of record."

The claims now pending and on appeal are claims 71-73, 75-78, 80-82 and 99 (set forth in Exhibit A), each of which stands rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a).

V. Status of the Amendments (37 C.F.R. § 1.192(c)(4))

No amendments were filed subsequent to the final rejection.

VI. Summary of the Invention (37 C.F.R. § 1.192(c)(5))

A. Concise Description of the Invention

ICAM-1, Intercellular Adhesion Molecule-1 (also known as the Human Rhinovirus Receptor Protein (HRRP)), was first identified as a receptor on endothelial cells mediating

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[1] The Examiner did not reiterate or address the rejection of claims 75-78 and 80-82 under 35 U.S.C. § 112, second paragraph. Therefore, Appellants have assumed that this rejection was withdrawn.

adhesion between endothelial cells and leukocytes by binding to Lymphocyte Function Associated Antigen (LFA-1) on the cell surface of leukocytes. It was subsequently determined that ICAM-1 is the cellular receptor for the human rhinovirus, a cause of the common cold in humans, as well as other related viruses. Human rhinoviruses have been found to gain entry into cells and mediate their infection by binding to ICAM-1 molecules present on cell surfaces. Thus, the administration of soluble ICAM-1 to an individual in need of treatment can effectively reduce the infectivity of rhinoviruses and other related viruses.

As currently claimed, the present invention is drawn to a purified or isolated ICAM-1 preparation or an artificial lipid membrane comprising purified or isolated ICAM-1, substantially free of natural contaminants, derived from human cells or tissues and capable of binding to LFA-1, Mac-1 or p150,95, wherein the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1. The purified or isolated ICAM-1 preparation has a certain molecular weight depending on the cell or tissue it was isolated from, as determined by SDS polyacrylamide gel electrophoresis.

Further details regarding the nature of the present invention are presented herein as necessary.

B. Support in the Specification for the Claims

Support for claims 71-73, 75-78 and 99, drawn to purified or isolated ICAM-1 preparations derived from human cells or tissues, substantially free of natural contaminants and capable of binding to LFA-1, Mac-1 or p150,95, wherein the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1, and wherein the purified or isolated

ICAM-1 preparation has a certain molecular weight depending on the cell or tissue it was isolated from, may be found in the specification at, *inter alia*, page 4, lines 8-19; Figures 5, 11, 12, 24 and 26 at pages 9-13; page 13, lines 4-10; page 16, lines 3-7; page 21, lines 3-28; page 51, lines 7-26; page 62, line 13 to page 66, line 10; page 79, lines 13-16; page 116, lines 25-29; page 119, line 31 to page 120, line 5; and page 142, lines 8-13.

Support for claims 80-82, drawn to an artificial membrane comprising purified or isolated ICAM-1 derived from human cells or tissues, substantially free of natural contaminants and capable of binding to LFA-1, Mac-1 or p150,95, wherein the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1, may be found in the specification at, *inter alia*, page 4, lines 8-19; Figures 5, 11, 12, 24 and 26 at pages 9-13; page 13, lines 4-10; page 16, lines 3-7; page 21, lines 3-28; page 51, lines 7-26; page 62, line 13 to page 66, line 10; page 79, lines 13-16; page 80, lines 29-33; Example 21 at pages 85-89; page 116, lines 25-29; page 119, line 31 to page 120, line 5; and page 142, lines 8-13.

VII. Issues (37 C.F.R. § 1.192(c)(6))

1. Whether claims 71-73, 75-78, 80-82 and 99 of the invention are unpatentable under 35 U.S.C. § 102(b) as anticipated by the Tomassini thesis, the Tomassini article or Colonno.

2. Whether claims 71-73, 75-78, 80-82 and 99 of the invention are unpatentable under 35 U.S.C. § 103(a) as obvious over the Tomassini thesis in view of the Tomassini article and/or Colonno.

VIII. Grouping of Claims (37 C.F.R. § 1.192(c)(7))

For the purpose of this appeal, the pending claims do not stand or fall together. The claims will be grouped as follows:

Group I: claims 71-73, 75-78 and 99 directed to a purified or isolated ICAM-1 preparation, substantially free of natural contaminants, derived from human cells or tissues and capable of binding to LFA-1, Mac-1 or p150,95, wherein the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1, and wherein the purified or isolated ICAM-1 preparation has a certain molecular weight depending on the cell or tissue it was isolated from, as determined by SDS polyacrylamide gel electrophoresis;

and

Group II: claims 80-82 directed to an artificial lipid membrane comprising purified or isolated ICAM-1, substantially free of natural contaminants, derived from human cells or tissues and capable of binding to LFA-1, Mac-1 or p150,95, wherein the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1.

IX. Arguments (37 CF.R. § 1.192(c)(8))

A. Issues

1. Anticipation

(a) The Final Rejection

The Examiner has finally rejected claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 102(b) in the Office Action of September 21, 2001 (Paper No. 30). The claims were rejected as being anticipated by the Tomassini thesis, the Tomassini article or Colonno. The Examiner's rationale, as presented in that Office Action, may be summarized as follows. In support of this rejection, the Examiner contends that "no more of the reference is required than that is sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced rhinovirus receptor." (Paper No. 30, at page 3.) The Examiner further stated that "[t]he burden is on the applicant to establish a patentable distinction between the claimed and referenced products." *Id.*

2. Obviousness

(a) The Final Rejection

The Examiner has finally rejected claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 103(a) in the Office Action of September 21, 2001. (Paper No. 30.) The claims were rejected as being unpatentable over the Tomassini thesis in view of the Tomassini article and/or Colonno. The Examiner's rationale, as presented in that Office Action (Paper No. 30), may be summarized as follows. According to the Examiner,

> [w]hile it is acknowledged that isolation and purification of an active form of a membrane-associated protein is dependent on the purification procedure used; it was certainly within the purview

> of the ordinary artisan to isolate and purify functional forms of a known [sic] at the time the invention was made, given the arsenal of isolation and purification methods known and practiced at the time the invention was made.

Id. at page 5. The Examiner further alleged that "applicant has failed to rebut prima facie showing of inherency or obviousness absent objective evidence such as side-by-side testing that would address the ability of the prior art HRV receptors ability to bind LFA-1/Mac-1/p150,95." (Paper No. 30, at page 6.)

The Examiner also stated that "[e]ven if there is an indication that there may be reduced binding of a particular radiolabeled HRV receptor preparation reduced binding to HRV [sic]; it maintained the ability to bind." (Paper No. 30, at page 6.)

The Examiner further stated that "[i]t is clear that the Tomassini thesis as well as the other references clearly teach that the HRV receptor is indeed the receptor for rhinovirus, that the HRV receptor is bound by antibodies that block HRV attachment or binding, and that the HRV receptor can be used as an immunogen to produce an antibody that blocks HRV attachment and binding." (Paper No. 30, at page 6.)

The Examiner additionally stated that "[e]ither it was inherent or expected at the time the invention was made that the HRV receptor identified and characterized by the references had the ability to bind virus and, in turn, would have either the inherent or expected properties of binding LFA-1/Mac-1/p150,95." (Paper No. 30, at page 6.)

Regarding claims 80-82, the Examiner stated that the Tomassini thesis, the Tomassini article and Colonno

> do not teach the use of artificial membranes per se. However, providing proteins of interest in artificial lipid membranes in a variety of means for a variety of purposes for the characterization

> and determination of the structure-function of a protein of interest was well known and practiced at the time the invention was made.

(Paper No. 28, at page 6.)

After providing a brief overview of the relevant law, Appellants will address the Examiner's rejections in turn.

B. Overview of Relevant Law

Anticipation

For a prior art reference to anticipate the claimed invention, it must disclose all of the elements of the claim, either expressly or inherently. *See Finnigan Corp. v. United States Int'l Trade Comm'n*, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1008 (Fed. Cir. 1999); *Key Pharms. Inc. v. Hercon Lab. Corp.*, 161 F.3d 709, 718, 48 USPQ2d 1911, 1919 (Fed. Cir. 1998). In addition, the reference must enable the claimed invention, thus putting it in the possession of the public. *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909, 107 S. Ct. 2490 (1987).

The first requirement for anticipation, strict identity between the claim and the prior art reference, is not met if a single element or limitation required by the claim is missing from the prior art source. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 USPQ 1264, 1271-72 (Fed. Cir. 1984). Where multiple prior art sources are required, the proper inquiry is whether the claimed invention meets the requirements for nonobviousness set forth in 35 U.S.C. §103(a). *See* 948 F.2d at 1267, 20 USPQ2d at 1748; 749 F.2d at 716, 223 USPQ at 1271 ("A prior art disclosure that 'almost' meets that standard may render the claim invalid under

§ 103, [but] it does not 'anticipate'.")(quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983)). However, it is not necessary for anticipation that the prior art reference use terminology identical to that used in the claim. *See In re Bond*, 910 F.2d 831, 832, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

A prior art reference is relevant for all that it teaches to those of ordinary skill in the art. *See In re Fritch*, 972 F.2d 1260, 1264, 23 USPQ2d 1780, 1782 (Fed. Cir. 1992). It is also well established that a single prior art reference may anticipate a claim even if certain claim limitations are not expressly found in the claim, if the limitations are inherent in the prior art reference. *See Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999).

> Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

Id. (internal citations omitted). The concept of inherent anticipation also applies to methods and processes. *See Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.* 246 F.3d 1368, 1376, 58 USPQ2d 1508, 1514 (Fed. Cir. 2001) ("[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent. . . .).

The second requirement for anticipation, that the reference enable the claimed invention, is determined from the viewpoint of a person of ordinary skill in the field of the invention. *See In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1675 (Fed. Cir. 1994). Thus, a prior art

reference is sufficiently enabling if one of ordinary skill in the art could have combined the teachings of the reference with his or her own knowledge to make the claimed invention. *See In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985); *In re Samour*, 571 F.2d 559, 562, 197 USPQ 1, 3-4 (CCPA 1978).

Obviousness

In determining whether the claimed subject matter is obvious in view of a combination of prior art references, Judge Rich, writing for the Federal Circuit in *In re Vaeck,* 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991), stated:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id. See also* MPEP § 2143.

Thus, if the prior art offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art, then a *prima facie* case of obviousness cannot be made. *In re Vaeck 20 U.S.P.Q.2d* at 1444. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531

(Fed. Cir. 1988) (citations omitted). Furthermore, "in determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *Id.* at 1531-32.

C. Appellants' Arguments

In the ensuing section, Appellants will address the Examiner's rejection (*see* Section IX, *supra*) for the two claim groups (*see* Section VIII, *supra*) separately, demonstrate that the pending claims in both groups are neither anticipated by the Tomassini thesis, the Tomassini article or Colonno, nor obvious over the Tomassini thesis, in view of the Tomassini article and/or Colonno, and explain why the Examiner's rejection should be reversed.

1. Group I (71-73, 75-78 and 99) claims are not anticipated by the Tomassini thesis, the Tomassini article or Colonno

Appellants' claimed invention is to a purified or isolated ICAM-1 (HRRP) preparation, wherein the ICAM-1 is in an active form, capable of binding to HRV, LFA-1, Mac-1 or p150,95. In contrast, the authors of the Tomassini thesis, the Tomassini article, and Colonno indicate that using their purification procedure, they are *unable* to isolate ICAM-1 in an active form. Since the Tomassini thesis, the Tomassini article or Colonno do not teach the isolation of ICAM-1 in an active form capable of binding to HRV, LFA-1, Mac-1 or p150,95, the claims are not anticipated by Tomassini or Colonno.

The isolation and purification of an *active* form of a membrane-associated protein, such

as ICAM-1, is highly dependent on the purification procedure used. Integral membrane proteins require high concentrations of detergent for solubilization and generally complete solubilization is needed to release them. Integral membrane proteins are normally neither soluble nor stable in the absence of detergent. *Current Protocols in Protein Science*, Strategies for Protein Purification, Unit 1.2 at 1.2.2 (1995). It is sometimes necessary to maintain natural phospholipids in association with the proteins in order to maintain activity. Furthermore, purification processes may be affected by the presence of detergents. *Id.*

Thus, the purification of membrane-associated proteins, such as ICAM-1, is not a trivial procedure. Moreover, there is no guarantee that any purification procedure will yield a *functional* form of ICAM-1, as presently claimed. In fact, the authors of the Tomassini thesis and article indicate that using their purification procedure, they are *unable* to isolate a functional 90-kDa receptor protein (ICAM-1) capable of binding virus (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.). Thus, the purification procedure taught by the Tomassini thesis and article renders the isolated HRRP preparation nonfunctional.

Not surprisingly, there are distinct differences between Tomassini's purification procedure and Appellants' procedure. One critical difference is the type of detergent used in the purification procedure. The detergent used by Tomassini *et al.* in their HRRP purification procedure is sodium deoxycholate (*see* page 39 of the Tomassini thesis and page 291 of the Tomassini article). Sodium deoxycholate is an ionic detergent. In contrast, the detergent used by Appellants in their ICAM-1 purification procedure is Triton X-100 (*see* page 62 of the specification). Triton X-100 is a non-ionic detergent. Ionic and non-ionic detergents can differ in their ability to denature proteins. See *Current Protocols in Protein Science*, Commonly Used Detergents, Appendix 1B

at A.1B.1 (1998) (copy attached to reply filed on March 21, 2002), stating that "[i]onic detergents are very good solubilizing agents, but they tend to denature proteins by destroying native three-dimensional structures." *Id.* at A.1B.2. Since the purification procedure used by Tomassini, employing an ionic detergent, renders their HRRP preparation nonfunctional, it is likely that their HRRP preparation was denatured to such an extent that it was not capable of binding to virus. In contrast, Appellants' HRRP preparation, which was purified using a non-ionic detergent, is functional and capable of binding to virus.

Based on the teachings of the Tomassini thesis and the Tomassini article, and the fact that the binding sites for LFA-1 and HRV overlap, one of ordinary skill in the art would have no reason to believe that Tomassini's purified HRRP preparation would bind to LFA-1, Mac-1, or p150,95. Therefore, the Tomassini thesis and the Tomassini article do not teach the isolation of HRRP in active form. One skilled in the art following the purification procedure outlined by Tomassini, would end up with a nonfunctional ICAM-1 preparation. The Examiner has not cited any art which teaches a purification procedure of ICAM-1 in which the ICAM-1 preparation retains the ability to bind HRV. Thus, the Tomassini thesis and article and Colonno article cited by the Examiner do not teach the isolation of a *functional* form of ICAM-1.

Appellants have also provided declaratory evidence that the teachings in the Tomassini thesis and article would indicate to the artisan of ordinary skill that the ICAM-1 preparation disclosed in Tomassini is nonfunctional since it is not capable of binding HRV. In his Declaration, Dr. Rothlein stated that

> in the Tomassini thesis and article, the authors indicate that "[r]epeated attempts to use radiolabeled HRV [human rhinovirus] in place of receptor antibody in the RIA gave inconclusive results owing to poor virus binding." (Tomassini thesis at 44, lines 9-12;

> and Tomassini article at 292, col. 2, lines 18-21.) The authors further indicate that "it is quite tempting to speculate that a pentamer of the 90-kDa receptor protein is needed for a functional receptor complex. This would correlate well with the 440-kDa receptor peak obtained by gel filtration and the inability to isolate a 90-kDa receptor protein capable of binding virus." (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.) These statements indicate that Tomassini's purified HRRP (ICAM-1) receptor preparation is not able to bind HRV. The most reasonable scientific explanation is that the purification procedures taught in the Tomassini thesis and Tomassini article disrupt or denature the HRRP receptor structure such that HRV binding is eliminated. Since the binding sites for HRV and LFA-1 overlap, one of ordinary skill in the art would expect that any disruption in structure from the purification procedure leading to the elimination of HRV binding, would also reduce or eliminate LFA-1 binding. Therefore, I do not believe that the HRRP preparation of Tomassini exhibits the ability to bind ligands, in contrast to the HRRP preparation recited in the pending claims, which does.

Rothlein Declaration at ¶ 6. Appellants note that the Examiner has not provided any specific reason or explanation to rebut the factual assertions made by Dr. Rothlein in the Rule 132 declaration (*see* Paper No. 28).

Additionally, the Tomassini thesis and article do not anticipate the claimed invention because they do not enable one skilled in the art to make and use the claimed invention. In fact, the authors of the Tomassini thesis and article indicate that using their purification procedure, they are unable to isolate a 90-kDa receptor protein (ICAM-1) capable of binding virus (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.) Specifically, the Tomassini thesis states that "it is quite tempting to speculate that a pentamer of the 90-kDa receptor protein is needed for a functional receptor complex. This would correlate well with the 440-kDa receptor peak obtained by gel filtration and the inability to isolate a

90-kDa receptor protein capable of binding virus." (Tomassini thesis at page 116, line 22, to page 117, line 1.) Thus, the purification procedures taught in the Tomassini thesis (and the Tomassini article) appear to disrupt the ICAM-1 receptor structure such that HRV binding activity is eliminated. Since the binding sites for HRV and LFA-1 overlap, one of ordinary skill in the art would expect that any disruption in structure from the purification procedure leading to the elimination of HRV binding, would also reduce or eliminate LFA-1 binding. Thus, the Tomassini thesis and the Tomassini article do not enable the isolation and characterization of an active form of ICAM-1, which is capable of binding to HRV, LFA1, Mac-1 or p150,95.

In addition, Colonno also does not teach the purification of an active form of ICAM-1. Colonno shows "a predominant protein band migrating with an apparent molecular weight of 90,000 (J. E. Tomassini and R. J. Colonno, submitted for publication)." (Colonno *et al.*, page 113, lines 29-31.) However, "[f]urther analysis of this candidate receptor protein is in progress." *Id.* at lines 34-35. Thus, Colonno mentions the Tomassini article discussed *supra* for further analysis of the receptor protein. As discussed above, neither the Tomassini article nor the Tomassini thesis teach the isolation of an active form of ICAM-1, capable of binding to HRV, LFA-1, Mac-1 or p150,95.

In contrast, Appellants' purification procedure taught in the specification enables isolation of a functional HRRP (ICAM-1) preparation, capable of binding to LFA-1, Mac-1 or p150,95. Since it is generally known in the art that activity of an isolated and purified protein depends primarily on the purification procedure used, the claimed functional limitations cannot be expected properties of the referenced rhinovirus receptor. Moreover, the art cited by the Examiner is proof that protein purification procedures do not result in the isolation of a

functional protein.

In sum, since neither the Tomassini thesis, the Tomassini article nor Colonno teach the isolation of ICAM-1 in active form as presently claimed, the claims are not anticipated by Tomassini or Colonno. Therefore, Appellants respectfully request the Board to reverse the Examiner's rejection of claims 71-73, 75-78 and 99 under 35 U.S.C. § 102(b).

2. Group II (80-82) claims are not anticipated by the Tomassini thesis, the Tomassini article or Colonno

As discussed *supra* for Group I claims, the cited art does not teach or enable the purification or isolation of an active form of ICAM-1, as presently claimed. Furthermore, the art cited by the Examiner does not teach an artificial lipid membrane comprising a purified or isolated ICAM-1 preparation capable of binding to LFA-1, Mac-1 or p150,95. Thus, for at least the reasons discussed above, claims 80-82 are not anticipated by Tomassini or Colonno. Therefore, Appellants respectfully request the Board to reverse the Examiner's rejection of claims 80-82 under 35 U.S.C. § 102(b).

3. Group I (71-73, 75-78 and 99) claims are nonobvious over the Tomassini thesis in view of the Tomassini article and/or Colonno

Appellants' claimed invention is to a purified or isolated ICAM-1 (HRRP) preparation, wherein the ICAM-1 is in an active form, capable of binding to HRV, LFA-1, Mac-1 or p150,95. In contrast, the authors of the Tomassini thesis, the Tomassini article, and Colonno indicate that using their purification procedure, they are *unable* to isolate ICAM-1 in an active form. Since

the Tomassini thesis in view of the Tomassini article and/or Colonno do not teach the isolation of ICAM-1 in an active form capable of binding to HRV, LFA-1, Mac-1 or p150,95, the claims are nonobvious over Tomassini in view of Colonno.

As Appellants previously indicated, the isolation and purification of an active form of a membrane-associated protein, such as ICAM-1, is highly dependent on the purification procedure used. Integral membrane proteins require high concentrations of detergent for solubilization and generally complete solubilization is needed to release them. Integral membrane proteins are normally neither soluble nor stable in the absence of detergent. Current Protocols in Protein Science, Strategies for Protein Purification, Unit 1.2 at 1.2.2 (1995). Thus, the purification of membrane-associated proteins, such as ICAM-1, is not a trivial procedure. Moreover, there is no guarantee that any purification procedure will yield a functional form of ICAM-1. In fact, the authors of the Tomassini thesis and article indicate that using their purification procedure, they are unable to isolate a functional 90-kDa receptor protein (ICAM-1) capable of binding virus (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.). Thus, one skilled in the art would have no reasonable expectation of success in producing an ICAM-1 preparation capable of binding to HRV, LFA-1, Mac-1 or p150,95.

As discussed *supra*, given the lack of success in obtaining a functional form of ICAM-1 using Tomassini's purification procedure, it was not clear at the time the invention was made that the HRV receptor identified in the references had the ability to bind virus. As the authors of the Tomassini thesis and the Tomassini article indicated, using their purification procedure, they were unable to isolate a 90-kDa receptor protein capable of binding virus. Since it is generally known in the art that activity of an isolated and purified protein depends primarily on the

purification procedure used, the claimed functional limitations *cannot* be expected properties of the referenced rhinovirus receptor. Thus, no side-by-side testing is necessary, since the references cited by the Examiner teach the isolation of an *inactive* form of HRRP *incapable* of binding to rhinovirus.

The Examiner stated that "[e]ven if there is an indication that there may be reduced binding of a particular radiolabeled HRV receptor preparation reduced binding to HRV [sic]; it maintained the ability to bind." (Paper No. 30, at page 6.) However, the Examiner is mistaken. There was no indication of *reduced* binding of the radiolabeled HRV receptor preparation to HRV; there was *no* binding. (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.) This lack of binding indicates that Tomassini's radiolabeled HRV receptor preparation is *inactive* and *incapable* of binding to virus.

The Examiner further stated that "[i]t is clear that the Tomassini thesis as well as the other references clearly teach that the HRV receptor is indeed the receptor for rhinovirus, that the HRV receptor is bound by antibodies that block HRV attachment or binding, and that the HRV receptor can be used as an immunogen to produce an antibody that blocks HRV attachment and binding." (Paper No. 30, at page 6.)

Appellants submit that it is not at all clear from the Tomassini thesis and the other references that the HRV receptor is the receptor for rhinovirus since the thesis does not teach the isolation and purification of an active form of ICAM-1 capable of binding to HRV, LFA-1, Mac-1 or p150,95. In addition, the thesis and references do not actually show that the HRV receptor preparation is bound by antibodies that block HRV attachment or binding. Instead, the thesis and references show, for example, that addition of increasing amounts of receptor

antiserum corresponded to an increased inhibition of ^{35}S-labeled rhinovirus binding to HeLa membranes. (Tomassini thesis at page 65, lines 4-8.). Moreover, the Examiner relies on no other reference to teach a method by which ICAM-1 may be purified.

Furthermore, it would not even have been possible to use the cDNA clones disclosed in the Tomassini thesis to obtain the ICAM-1 protein. Dr. Rothlein, in his Rule 132 Declaration, discussed the fact that the cDNA clones disclosed in the Tomassini thesis would not express ICAM-1, and that the clones represent a cloning artifact or a fortuitous cross-reactivity of the anti-HRV-receptor antibody with another anti-ICAM-1 protein. (Rothlein Declaration at ¶ 9.) As Dr. Rothlein noted:

> As further evidence that the Tomassini clones do not comprise the actual ICAM-1 gene, I note that a subsequent article published by the author of the thesis, Tomassini *et al.*, *Proc. Natl. Acad. Sci. 86*:4907-4911 (1989) (not prior art), teaches the cloning of the ICAM-1 gene. A copy of this article is attached hereto as Exhibit H. To obtain the cloned gene, Tomassini *et al.* used a different cDNA library and different clones than the library and clones described in the thesis. In my opinion, if the clones described in the thesis actually contained the ICAM-1 gene, it would not have been necessary to clone the ICAM-1 gene from another source. Finally, I note that the monoclonal antibody directed against the HRV receptor (ICAM-1) did not recognize the protein expressed from clone 4A, showing that the portion of ICAM-1 recognized by the antibody was not expressed in its native state. (Tomassini thesis at 85, lines 16-20.)

Id. at ¶¶ 9 and 10.

The Examiner also stated that "[e]ither it was inherent or expected at the time the invention was made that the HRV receptor identified and characterized by the references had the ability to bind virus and, in turn, would have either the inherent or expected properties of binding LFA-1/Mac-1/p150,95." (Paper No. 30, at page 6.)

As discussed *supra*, it was neither inherent nor expected at the time the invention was made that the HRV receptor identified in the references had the ability to bind virus, since the authors of the Tomassini thesis and the Tomassini article indicated that using their purification procedure, they were unable to isolate a 90-kDa receptor protein capable of binding virus. Since it is generally known in the art that activity of an isolated and purified protein depends primarily on the purification procedure used, the claimed functional limitations *cannot* be expected properties of the referenced rhinovirus receptor. Moreover, one with ordinary skill in the art would have no reason to expect that their HRRP purification procedure would yield a functional form of HRRP capable of binding to LFA-1, Mac-1, or p150,95, since the references cited by the Examiner teach the isolation of an *inactive* form of HRRP *incapable* of binding to rhinovirus.

In contrast, Appellants' claimed invention relates to an isolated or purified ICAM-1 preparation, capable of binding to LFA-1, Mac-1 or p150,95. As Dr. Rothlein stated

> [t]he authors of the Tomassini thesis and the Tomassini article indicate that they are unable to isolate a 90-kDa receptor protein that is capable of binding virus. Thus, I believe that one of ordinary skill in the art would have no reason to expect that Tomassini's or their ICAM-1 purification procedure would yield ICAM-1 capable of binding to HRV. Furthermore, in my opinion, based on the teachings of the Tomassini thesis and the Tomassini article, and the fact that the binding sites for LFA-1 and HRV overlap, one of ordinary skill in the art would thus have no reason to believe that their purification procedure would yield HRRP (ICAM-1) capable of binding to LFA-1, Mac-1, or p150,95.

Rothlein Declaration at ¶ 7.

In sum, the ICAM-1 preparation taught by Tomassini differs from the ICAM-1 preparation recited in Appellants' claims because, *inter alia*, it is not capable of binding to rhinovirus, LFA-1, Mac-1, or p150,95. Colonno does not remedy the deficiencies of the

Tomassini thesis and article because it also does not teach the purification or isolation of a functional form of ICAM-1. Since the art relied upon by the Examiner does not teach all aspects of the invention as presently claimed, *e.g.*, ICAM-1 capable of binding to LFA-1, Mac-1, or p150,95, the Examiner has failed to establish a *prima facie* case of obviousness.

In sum, the Examiner has committed reversible error by failing to consider all of the evidence of record that is relevant to the issue of nonobviousness and has not established a *prima facie* case of obviousness. Therefore, Appellants respectfully request the Board to reverse the Examiner's rejection of claims 71-73, 75-78 and 99 under 35 U.S.C. § 103(a).

4. Group II (80-82) claims are nonobvious over the Tomassini thesis in view of the Tomassini article and/or Colonno

In view of the deficiencies of the Tomassini thesis and article which Appellants have described (*see* Section IX.C.3 *supra*), the artificial lipid membranes comprising purified or isolated ICAM-1 as claimed in claims 80 and 82 are nonobvious. Appellants also contend that the Group II claims are nonobvious over Tomassini in view of Colonno for the following reasons.

In order to establish a prima facie case of obviousness, the Examiner must establish that all elements of the claimed invention are present in the prior art. Thus, to render claims 80-82 obvious, the Examiner must establish that the prior art teaches or suggests an artificial lipid membrane comprising purified or isolated ICAM-1 capable of binding to LFA-1, Mac-1 or p150,95. Tomassini does not teach the purification or isolation of an active form of ICAM-1. Furthermore, the art cited by the Examiner does not teach artificial lipid membranes comprising an active form of a purified or isolated ICAM-1 preparation. Therefore, the Examiner has failed

to establish a *prima facie* case of obviousness.

In sum, the Examiner has committed reversible error by failing to consider all of the evidence of record that is relevant to the issue of nonobviousness and has not established a *prima facie* case of obviousness. Accordingly, the Examiner's rejection of claims 80-82 under 35 U.S.C. § 103(a) should be reversed.

X. Summary

It is submitted that the Examiner's rejection of claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) is erroneous. Appellants contend that the Examiner's failure to consider all of the relevant evidence regarding the cited art and nonobviousness of the claimed invention is reversible error. Accordingly, the Board is respectfully requested to reverse the Examiner and remand this application for issuance.

Respectfully submitted,

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Appendix of the Claims (37 C.F.R. § 1.192(e)(7))

71. A purified or isolated ICAM-1 preparation substantially free of natural contaminants, wherein said purified or isolated ICAM-1 is derived from human cells or tissues and is capable of binding to LFA-1, Mac-1, or p150,95; and wherein said purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1.

72. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 can bind LFA-1.

73. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 can specifically bind LFA-1.

75. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is human spleen ICAM-1 having a molecular weight of 72 to 91 kDa as determined by SDS polyacrylamide gel electrophoresis.

76. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is ICAM-1 of JY B-lymphoblastoid cells having a molecular weight of 76.5 to 97 kDa as determined by SDS polyacrylamide gel electrophoresis.

77. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is ICAM-1 of a myelomonocytic cell line having a molecular weight of 114 kDa as determined by SDS polyacrylamide gel electrophoresis.

78. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is fibroblast ICAM-1 having a molecular weight of 97 kDa as determined by SDS polyacrylamide gel electrophoresis.

80. An artificial lipid membrane comprising purified or isolated ICAM-1, wherein said purified or isolated ICAM-1 is derived from human cells or tissues, is substantially free of natural protein contaminants in said artificial lipid membrane, and is capable of binding to LFA-1, Mac-1, or p150,95; and wherein said purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1.

81. An artificial membrane as claimed in claim 80, wherein said purified or isolated ICAM-1 binds to LFA-1.

82. The lipid membrane as claimed in claim 80, wherein said lipid membrane is an artificial planar membrane.

99. The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 can bind p150,95.